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EXAMINER	
RAWLINGS, STEPHEN L	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/076,905	RONAI, ZE'EV	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 August 2004 and 18 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *5-7, 16-19, 22, and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8-15,20,21 and 23-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20020522;20021011*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *IDS:20040812*.

DETAILED ACTION

1. The reply filed August 17, 2004 is acknowledged and has been entered.

2. The election filed May 18, 2004 is acknowledged and has been entered. Applicant has elected the invention of Group I, claims 1-4, 8-15, and 20-29, insofar as the claims are drawn to a polypeptide, a pharmaceutical composition comprising said polypeptide, and a method for inhibiting growth of a tumor comprising introducing or administering said composition. In addition, Applicant has elected the species of invention wherein said tumor cell is a melanoma tumor cell.

Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

3. Claims 1-32 are pending in the application. Claims 5-7, 16-19, 22, and 30-32 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

4. Claims 1-4, 8-15, 20, 21, and 23-29 are currently under prosecution.

Election/Restrictions

5. The requirement to elect a species of invention by selecting the tumor cell from the group consisting of a melanoma tumor cell and a breast cancer tumor cell, as set forth in section 5 of the Office action mailed March 18, 2004, has been withdrawn.

6. At page 6 of the reply filed May 18, 2004, Applicant has remarked:

> Applicants note that claim 22, included by the Examiner in Group 1, is not directed to a polypeptide or method of use thereof and may not have been intended by the Examiner to be in Group 1. Accordingly, Applicants withdraw this claim from consideration. In addition, since elected claim 23, as a multiple dependent claim, depends partly from claim 22, claim 23 is amended herein to remove the dependency from claim 22.

As Applicant has suggested, the Examiner inadvertently included claim 22 in Group I. Since claim 22 is drawn to a pharmaceutical composition comprising the vector of claim 18, the claim is properly grouped in Group II only, not in Group I. Accordingly, Group I now includes only claims 1-4, 8-15, 20, 21, and 23-29.

The Examiner notes his appreciation of Applicant's remarks, which serve to clarify the record.

Information Disclosure Statement

7. The information disclosures filed May 22, 2002, October 11, 2002, and August 12, 2004 has been considered. An initialed copy of each is enclosed.

Specification

8. The disclosure is objected to because the disclosure refers to embedded hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified. Reference to hyperlinks and/or other forms of browser-executable code and to the Internet contents so identified is impermissible and therefore requires deletion.

An example of such a disclosure appears in the specification at page 64, line 1.

The attempt to incorporate essential or non-essential subject matter into the patent application by reference to a hyperlink and/or other forms of browser-executable code is considered to be an improper incorporation by reference. See MPEP § 608.01(p), paragraph I regarding acceptable incorporation by reference. See 37 CFR § 1.57.

9. The specification is objected to because the use of improperly demarcated trademarks has been noted in this application. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be

respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Examples of such improperly demarcated trademarks include Adriamycin™ (page 39, line 10), CellQuest™ (page 40, line 11), and GenePix™ (page 63, line 27).

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

10. The specification is objected to because of the following informality:
"Clontech" is misspelled as "Clonetech" at page 17, line 16.
Appropriate correction is required.

Claim Objections

11. Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim or amend the claim to place the claim in proper dependent form. Claim 4 depends from claim 3, which depends from claim 2. Claim 4 recites the same limitation as that recited in claim 3 without reciting further limitations. Accordingly, claims 3 and 4 are identical in scope, so therefore claim 4 does not further limit the subject matter of claim 3.

12. Claim 4 is further objected to under 37 CFR 1.75 as being a substantial duplicate of claim 3. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is

proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Again, claim 4 depends from claim 3, which depends from claim 2. Claim 4 recites the same limitation as that recited in claim 3 without reciting further limitations. Accordingly, claims 3 and 4 are identical in scope.

13. Claim 14 is objected to because "about" is misspelled as "aobut" in line 2. Appropriate correction is required.

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 1, 2, 8-13, 15, 20, 21, and 23-29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 8-12 are drawn to a method for inhibiting growth of a tumor cell comprising inhibiting transcriptional activity of ATF2. It is duly noted that claims 1 and 8-12 are not limited to methods comprising administering any one particular agent capable of inhibiting the transcriptional activity of ATF2. Accordingly, claims 1 and 8-12 are directed to a genus of agents capable of inhibiting the transcriptional activity of ATF2, which vary markedly in both structure and function. For example, the genus includes small organic molecules, antibodies, and ligands that bind ATF2 or any other factor involved in ATF2-regulated transcription (e.g., p38), which inhibits directly or indirectly the transcriptional activity of ATF2. Accordingly, there is no correlation

between any one particularly identifying structural feature, which is common among at least a substantial number of the members of the genus of agents capable of inhibiting the transcriptional activity of ATF2, and their common function. As such, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus of agents suitable for use in practicing the claimed invention. Therefore, the specification would not reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed.

Claims 2, 13, 15, 20, 21, and 23-29 are directed to a genus of polypeptide comprising "an N-terminal antagonist fragment of ATF2" or "an inhibitory ATF2 N-terminal fragment", either of which is deemed an equivalent of the other. At page 9, lines 18-20, the specification defines the term "inhibitory ATF2 N-terminal fragment" as "an N-terminal polypeptide fragment of ATF2 that inhibits ATF2 activity, and which excludes full-length ATF2"; and the specification defines "inhibition of ATF2 activity" as including inhibiting ATF2-regulated transcription, inhibiting tumor cell growth, increasing apoptosis, increasing sensitivity of tumor cells, in particular, to UV irradiation or treatments with chemotherapeutic agents (page 9, line 29, through page 30, line 6).

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, ``Written Description'' Requirement (66 FR 1099-1111, January 5, 2001) state, "[p]ossession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). The *Guidelines* further state, "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species *cannot* be achieved by disclosing only one species within the genus" (Id. at 1106); accordingly, it follows that an adequate written description of a genus cannot be achieved in the absence of a disclosure of at least one species within the genus. Because the claims encompass a genus of variant species, an adequate written description of the claimed invention must

include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant had possession of the claimed invention at the time the application was filed.

The specification teaches that a peptide comprising amino acids 50-100 (i.e., "Peptide II") of ATF2 inhibits ATF2 activity; see, e.g., page 9, lines 26-28. The specification teaches that three other N-terminal peptide fragments of ATF2, namely "Peptide I" (amino acids 1-50), "Peptide III (amino acids 100-150), and "Peptide IV" (amino acids 150-200) were selected for initial analysis (see, e.g., page 39, lines 17-19; and page 40, lines 28 and 29), but only Peptides II and IV were selected for further analysis on the basis of their pronounced effect on late-stage melanoma cell lines (page 49, lines 10-13). Furthermore, the specification teaches that of the remaining peptides, only Peptide II efficiently increased sensitivity of tumor cells to the cytotoxic effects of UV-irradiation and treatments with chemotherapeutic agents (see, e.g., page 49, lines 13-19); conversely, the specification teaches that Peptide IV increased the resistance of melanoma cells to UV- and drug-induced apoptosis (see, e.g., page 50, line 22-24).

The specification teaches that each peptide of the four peptides initially selected for analysis is derived from the amino acid sequence of the trans-activating domain of ATF2 and comprises the phosphoacceptor sites for p38 and JNK (amino acids 69 and 71) and the region required for ATF2-intramolecular inhibition (page 41, lines 1-8). The specification teaches that, since the level of ATF2 phosphorylation was reduced in UV-treated Peptide II-expressing melanoma cells, it appears that Peptide II decreases phosphorylation of endogenous ATF2, thus rendering endogenous ATF2 inactive (page 50, lines 10-21). Because Peptide II (amino acids 50-100) comprises the two residues (amino acids 69 and 71) that are phosphorylated by the kinases p38 and JNK upon the

activation of ATF2, it appears that this structural feature correlates with the ability of a peptide to inhibit the activity of ATF2, as defined in the specification at page 9, line 29, through page 30, line 6. This conclusion is further supported by the teachings of the prior art. For example, Duyndam et al. (*Oncogene*. 1999; **18**: 2311-2321) teaches that a "dominant-negative" mutant ATF2 molecule, in which the threonines at positions 69 and 71 were replaced by alanines, completely inhibits p300-induced *c-jun* promoter activity; see entire document (e.g., page 2317, column 2). Consistently, the specification teaches that earlier studies in their laboratory revealed that phosphorylation-deficient full length ATF2 has similar effects to those of the amino-terminal truncated form of ATF2, which serves as a dominant negative, since both efficiently down-regulated expression of TNFα (page 50, lines 18-21).

Therefore, the specification adequately describes only members of the genus of polypeptides comprising "an N-terminal antagonist fragment of ATF2" or "an inhibitory ATF2 N-terminal fragment", which comprise amino acids 50-100, since only Peptide II (amino acids 50-100) is described as capable of inhibiting ATF2 activity. The specification has not described members of the genus of polypeptides comprising "an N-terminal antagonist fragment of ATF2" or "an inhibitory ATF2 N-terminal fragment", which do not comprise amino acids 50-100, or more particularly, which do not comprise amino acids 69 and 71, and which do not compete with endogenous ATF2 for activating kinase activity.

In deciding *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the Court held that a generic statement that defines a genus of nucleic acids *by only their functional activity* does not provide an adequate written description of the genus. By analogy, a generic statement that defines a genus of polypeptides by only their common ability to inhibit ATF2 activity and particularly, the transcriptional activity thereof, does not serve to adequately describe the genus as whole. The Court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a precise definition of a representative number of members of the genus, such as by reciting the structure, formula, chemical name, or physical properties of those members, rather than

by merely reciting a wish for, or even a plan for obtaining a genus of molecules having a particular functional property. The recitation of a functional property alone, which must be shared by the members of the genus, is merely descriptive of what the members of genus must be capable of doing, not of the substance and structure of the members.

16. Claims 1 and 8-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting growth of a tumor cell by a process that comprises inhibiting the transcriptional activity of ATF2 by introducing a polypeptide comprising an N-terminal antagonist fragment of ATF2, does not reasonably provide enablement for inhibiting growth of a tumor cell by a process that comprises inhibiting the transcriptional activity of ATF2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The amount of guidance, direction, and exemplification disclosed by Applicant would not be sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation. Factors to be considered in determining whether undue experimentation is required are summarized in *Ex parte Forman*, 230 USPQ 546 (BPAI 1986). These factors include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

As explained above, claims 1 and 8-12 are drawn to a method for inhibiting growth of a tumor cell comprising inhibiting transcriptional activity of ATF2, but the claims are not limited to methods comprising introducing or administering any one particular agent capable of inhibiting the transcriptional activity of ATF2. Accordingly, claims 1 and 8-12 are directed to a genus of agents capable of inhibiting the transcriptional activity of ATF2, which vary markedly in both structure and function.

For example, the genus includes small organic molecules, antibodies, and ligands that bind ATF2 or any other factor involved in ATF2-regulated transcription (e.g., p38), which inhibits directly or indirectly the transcriptional activity of ATF2. Accordingly, there is no correlation between any one particularly identifying structural feature, which is common among at least a substantial number of the members of the genus of agents capable of inhibiting the transcriptional activity of ATF2, and their common function. As such, the skilled artisan could not immediately envision, recognize, or distinguish at least a substantial number of the members of the genus of agents suitable for use in practicing the claimed invention without the need to first perform an undue amount of additional experimentation. Apart from that which is taught by the prior art, one cannot make and then use what has not been adequately described in the specification.

The specification teaches a peptide comprising amino acids 50-100 (e.g., Peptide II) is capable of inhibiting the activity of ATF2 and can be used to inhibit the growth of tumor cells. This amount of guidance, direction, and exemplification is not reasonably commensurate in scope with that of the claims.

In deciding *In re Fisher*, 1666 USPQ 19 24 (CCPA 1970), the Court indicated the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. It has been well known to those skilled in the art at the time the invention was made that minor structural differences among structurally related compounds or compositions could result in substantially different biological and pharmacological activities. The specification does not teach the skilled artisan to make any other substances, which can be used to practice the claimed invention; and the skilled artisan cannot predict whether any given substance can be used to successfully practice the claimed invention. Defining a substance by its principal biological activity amounts to an alleged conception having no more specificity than that of a wish to know the identity of any material with that biological property. See *Colbert v. Lofdahl*, 21 USPQ2d, 1068, 1071 (BPAI 1992). Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. Therefore, the overly broad scope of the claims would merely serve as an invitation to one skilled in the art to identify a substance having the ability to inhibiting or enhancing angiogenesis and

neovascularization by microvascular endothelial cells, which can be used to practice the claimed invention. The Court has decided:

> Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.

Genentech Inc. v. Novo Nordisk A/S, 42 USPQ2d 1001, 1005 (CAFC 1997).

The prior art teaches some other therapeutic agents that are used to inhibit, for example, the transcription activity of ATF2 or to sensitize tumor cells to the cytotoxic effects of irradiation. For example, Ivanov et al. (*Oncogene*. 2000; **19**: 3003-3012) (of record) teaches the p38 pharmacological inhibitor, SB203580 inhibits the growth of tumor cells by sensitizing the tumor cells to UV-irradiation; see entire document (e.g., page 3005, column 2). Furthermore, Duyndam et al. (cited *supra*) teaches that a "dominant-negative" mutant ATF2 molecule, in which the threonines at positions 69 and 71 were replaced by alanines, completely inhibits p300-induced *c-jun* promoter activity (see, e.g., page 2317, column 2); the specification teaches that earlier studies in their laboratory revealed that such dominant negative mutants of ATF2 efficiently down-regulate expression of TNFα (page 50, lines 18-21); and US Patent No. 6,579,856 B2 teaches inhibiting cancer by a process comprising administering a dominant negative mutant of ATF2, which inhibits the transcriptional activity of ATF2.

However, even given that which is well known in the art, apart from a polypeptide comprising amino acids 50-100, and more particularly comprising the two residues (amino acids 69 and 71) that are phosphorylated by the kinases p38 and JNK upon the activation of ATF2, which is capable of inhibiting the activity of ATF2, and apart from the specification does not provide sufficient guidance, direction, and exemplification to enable the skilled artisan to make and use the claimed invention, since the claims are drawn to the use of an undisclosed agent capable of inhibiting transcriptional activity of ATF2 and the genus of such agents includes members that vary substantially in both structure and function (i.e., the mechanism or mode by which ATF2 activity is inhibited).

The arts of pharmacology, drug discovery, and cancer therapy are highly unpredictable and complex in nature, in part, because of the inherent limitations of using

animal and cell models in drug discovery and pharmacological testing, since the results of such studies often cannot be extrapolated to reliably and accurately predict the effectiveness of the drugs in humans. Gura (*Science*. 1997; **278**: 1041-1042), for example, discusses the limitations of animal and cell models. Gura teaches that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models, but that only 39 have actually been shown to be useful for chemotherapy (page 1041, first and second paragraphs). Sadly, Gura reports that using xenograft animal models to evaluate the potential of novel antitumor therapies often leads to the discovery of " 'good mouse drugs rather than good human drugs' " (page 1041, column 2), because the results acquired using animal models or cell culture are not correlative with those acquired in the clinic.

In conclusion, upon careful consideration of the factors used to determine whether undue experimentation is required, in accordance with *Ex parte Forman*, 230 USPQ 546 (BPAI 1986), the amount of guidance, direction, and exemplification disclosed by Applicant is not deemed sufficient to enable the skilled artisan to use the claimed invention without a need to perform an undue amount of additional experimentation.

Claim Rejections - 35 USC § 102

17. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

18. Claims 1-4, 8-10, 12-14, 20, 23-26, and 29 are rejected under 35 U.S.C. 102(e) as being anticipated by US Patent No. 6,579,856 B2, as evidenced by van Dam et al. (*EMBO J.* 1995 Apr 18; **14** (8): 1798-1811).

As evidenced by van Dam et al., US Patent No. 6,579,856 B2 ('856) teaches a method for treating a tumor in a subject by increasing the sensitivity of the tumor cells to a cancer therapy by contacting the tumor cells with a dominant negative mutant of ATF2 comprising the minimal transactivation domain at the amino-terminus of ATF2; see entire document (e.g., the abstract; column 6, lines 27-47; column 12, lines 5-31; column 13, lines 53-55; column 15, lines 53-62; claims 5 and 8). '856 teaches the process comprises inhibiting transcription regulated by ATF2; see, e.g., column 6, lines 59-66. '856 teaches the dominant negative mutant of ATF2 is prepared according to the teachings of van Dam et al. (*EMBO J.* 1995 Apr 18; **14** (8): 1798-1811); see column 12, lines 18-21. '856 teaches pharmaceutical compositions comprising pharmaceutically acceptable carriers or excipients; see, e.g., column 13, lines 53-67. '856 teaches the tumor cell can be a melanoma cell or a breast cancer cell; see column 15, lines 53-60. '856 teaches the process comprises radiotherapy and/or chemotherapy, as '856 teaches that, in order to improve therapeutic advantage, therapies are often used in combination; see, e.g., column 2, lines 56-65; and column 16, lines 24-29. Moreover, '856 teaches that the process allows a lower dose of a conventional therapeutic modality, such as radiation or chemotherapy, to be used; see, e.g., column 16, lines 24-29.

van Dam et al. teaches a dominant negative mutant of ATF2 comprising the minimal transactivation domain at the amino-terminus of ATF2; see entire document (e.g., page 1809, column 2). van Dam et al. teaches the mutant protein comprises amino acids 19-96 of ATF2. Thus, absent a showing of any difference, van Dam et al. teaches a polypeptide that is deemed the same as the polypeptide to which the clams are directed, since van Dam et al. teaches a polypeptide comprising an inhibitory ATF2 N-terminal fragment having a sequence consisting of from about amino acid 50 to about amino acid 100 of ATF2.

Claim Rejections - 35 USC § 103

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claim 1, 10, 11, 23, and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,579,856 B2, as evidenced by van Dam et al. (*EMBO J.* 1995 Apr 18; **14** (8): 1798-1811), in view of Ivanov et al. (*Oncogene*. 2000; **19**: 3003-3012) (of record).

Claim 1, 10, and 11 are drawn to a method for inhibiting the growth of a tumor cell comprising inhibiting the transcriptional activity of ATF2 and further treating the tumor cell with the chemotherapeutic agent SB203580. Claims 23 and 26-28 are drawn to a method for treating a tumor in a subject comprising administering a composition comprising a polypeptide comprising an inhibitory ATF-2 N-terminal fragment and further treating the tumor with the p38 inhibitor SB203580.

As evidenced by van Dam et al., US Patent No. 6,579,856 B2 ('856) teaches that which is set forth in the rejection of 1-4, 8-10, 12-14, 20, 23-26, and 29 under 35 USC § 102 above.

However, '856 does not expressly teach or suggest treating the tumor cells with the p38 inhibitor SB203580 (claims 11, 27, and 28).

Ivanov et al. teaches the p38 pharmacological inhibitor, SB203580 inhibits the growth of tumor cells by sensitizing the tumor cells to UV-irradiation; see entire document (e.g., page 3005, column 2).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have treated tumor cells by a process comprising administering to a patient having a tumor a composition comprising a dominant negative mutant of ATF2, according to '856, and further treating the tumor by administering to the patient

an effective dose of SB203580 to sensitize the tumor cells to UV-irradiation, because '856 teaches, in order to improve therapeutic advantage, therapies are often used in combination, and moreover because '856 teaches a dominant negative mutant of ATF2 sensitizes tumor cells to radiotherapy, whereas Ivanov et al. teaches SB203580 sensitizes tumor cells to radiotherapy. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to treat a tumor with an improved therapeutic advantage. One ordinarily skilled in the art at the time of the invention would have had a reasonable expectation of success in doing so, since the prior art teaches that both the mutant protein and SB203580 sensitize tumor cells to the cytotoxic effects of irradiation.

21. Claims 13, 15, 21, 23-26, and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,579,856 B2, as evidenced by van Dam et al. (*EMBO J.* 1995 Apr 18; **14** (8): 1798-1811), in view of US Patent No. 6,335,178 B1.

Claim 13, 15, and 21 are drawn to a polypeptide comprising an inhibitory ATF2 N-terminal fragment and a translocation peptide sequence, or a composition thereof, which further comprises a pharmaceutically acceptable carrier or excipient. Claims 23-26, and 29 are drawn to a method for treating a tumor in a subject comprising administering a composition comprising a polypeptide comprising an inhibitory ATF-2 N-terminal fragment and a translocation peptide sequence.

As evidenced by van Dam et al., US Patent No. 6,579,856 B2 ('856) teaches that which is set forth in the rejection of 1-4, 8-10, 12-14, 20, 23-26, and 29 under 35 USC § 102 above.

However, '856 does not expressly teach or suggest a polypeptide comprising an inhibitory ATF-2 N-terminal fragment and a translocation peptide sequence (claim 15).

US Patent No. 6,335,178 B1 ('178) teaches methods for facilitating the production of recombinant proteins in host cells by fusing the polynucleotide sequence encoding a protein to the polynucleotide sequence encoding the amino acid sequence of a translocation signal sequence; see entire document (e.g., column 21, lines 19-48). '178 teaches the method facilitates purification and increases the yield of functional

proteins of interest, since the recombinant protein is translocated into the periplasm; see, e.g., the abstract; column 1, lines 16-42; column 10, lines 28-43.

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to produce a dominant negative mutant of ATF2, according to '856, by the methodology described by '178, since '178 teaches the method facilitates purification and increases the yield of functional proteins of interest. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to produce the polypeptide.

22. Claims 27 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 6,579,856 B2, as evidenced by van Dam et al. (*EMBO J.* 1995 Apr 18; **14** (8): 1798-1811), in view of US Patent No. 6,335,178, as applied to claim 13, 15, 21, 23-26, and 29 above, and further in view of Ivanov et al. (*Oncogene*. 2000; **19**: 3003-3012).

Claims 27 and 28 are drawn to a method for treating a tumor in a subject comprising administering a composition comprising a polypeptide comprising an inhibitory ATF-2 N-terminal fragment and a translocation peptide sequence, and further treating the tumor with SB203580.

As evidenced by van Dam et al., US Patent No. 6,579,856 B2 ('856) teaches that which is set forth in the rejection of 1-4, 8-10, 12-14, 20, 23-26, and 29 under 35 USC § 102 above; and US Patent No. 6,335,178 B1 teaches that which is set forth in the rejection of claims 13, 15, 21, 23-26, and 29 under 35 USC § 103 above.

However, neither '856 nor '178 expressly teaches or suggests treating the tumor cells with the p38 inhibitor SB203580 (claims 27 and 28).

Ivanov et al. teaches the p38 pharmacological inhibitor, SB203580 inhibits the growth of tumor cells by sensitizing the tumor cells to UV-irradiation; see entire document (e.g., page 3005, column 2).

It would have been *prima facie* obvious to one ordinarily skilled in the art at the time of the invention to have treated tumor cells by a process comprising administering to a patient having a tumor a composition comprising a polypeptide comprising a

dominant negative mutant of ATF2, according to '856, and a translocation signal sequence, according to '178, and further treating the tumor by administering to the patient an effective dose of SB203580 to sensitize the tumor cells to UV-irradiation, because '856 teaches, in order to improve therapeutic advantage, therapies are often used in combination, and moreover because '856 teaches a dominant negative mutant of ATF2 sensitizes tumor cells to radiotherapy, whereas Ivanov et al. teaches SB203580 sensitizes tumor cells to radiotherapy. One ordinarily skilled in the art at the time of the invention would have been motivated to do so to treat a tumor with an improved therapeutic advantage. One ordinarily skilled in the art at the time of the invention would have had a reasonable expectation of success in doing so, since the prior art teaches that both the mutant protein and SB203580 sensitize tumor cells to the cytotoxic effects of irradiation.

Conclusion

23. No claims are allowed.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
December 17, 2004